

FIG. 1

Anatomy of an Intron

MAG **GURAGU** - - - - **YNYURAY** - - **Y₁₂₋₁₅NC AG** **G**

5' Splice Site
(Splice Donor)

Branch

3' Splice Site
(Splice Acceptor)

M = C or A

R = puRine (A or G)

Y = pYrimidine (C or T or U)

Conservative Mutagenesis of Near Consensus 3' Splice sequence

TTC TCA GGA GAA
Phe Ser Gly Glu

Alternate Codons	
Ser	Gly
TCC	None
TCG	
TCT	

FIG. 3

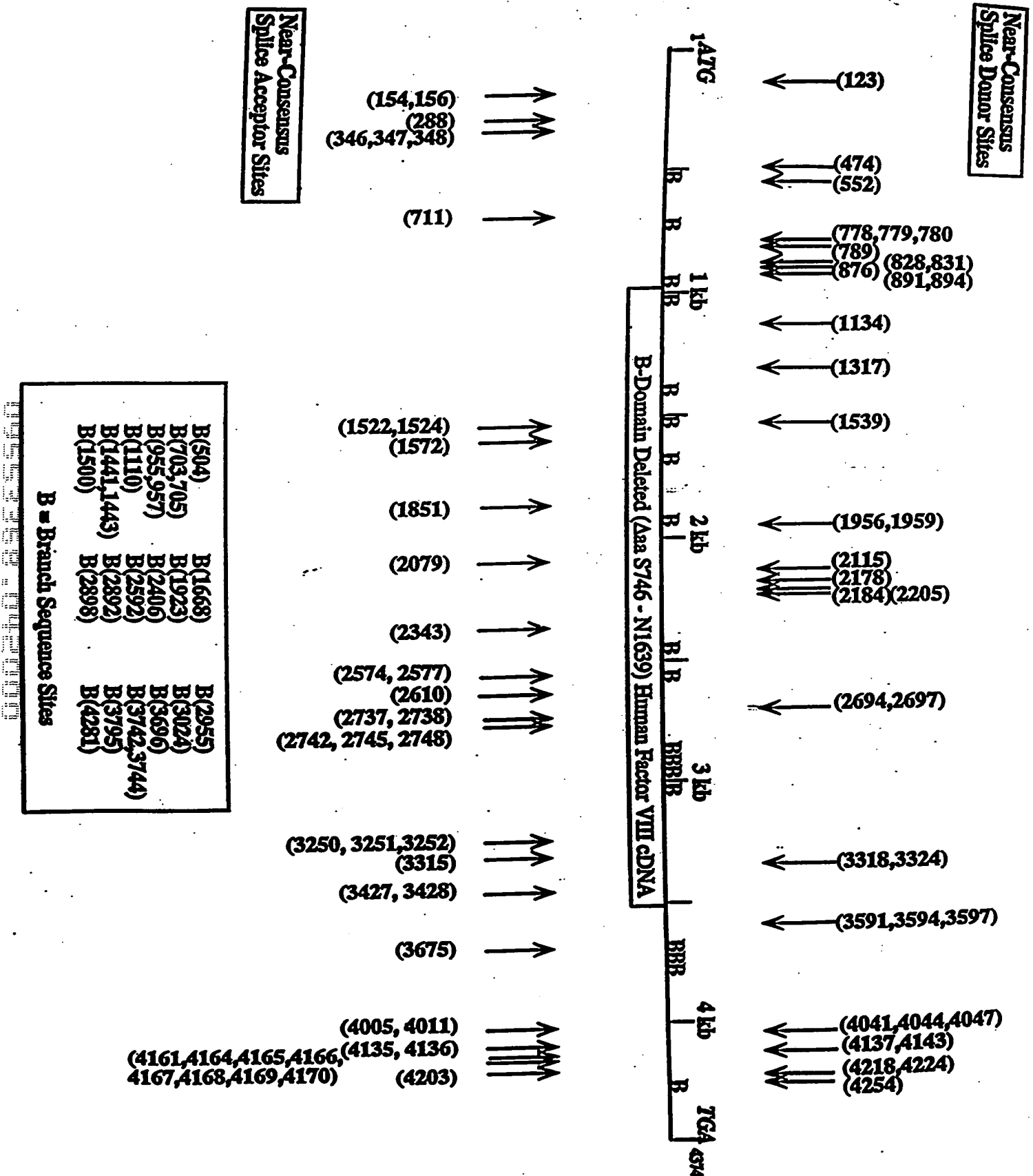


FIG. 4A

NC-Splice Donor Changes:

Location in Bayer BDD-Factor VIII cDNA	Nucleotide Change	Codon	Amino Acid
123	T → A	GGA	G
474	G	CAA	Q
552	T	GTT	V
778	T	AGC	S
779	C	AGC	S
780	T	AGC	S
789	T	GGA	G
828	G	GTT	V
831	T	ATA	I
876	T	GGA	G
891	G	GTT	V
894	G	AGA	R
1134	G	AGA	R
1317	T	GGA	G
1539	T	GGA	G
1956	G	GAA	E
1959	G	GTA	V
2115	G	GGA	G
2178	G	AAA	K
2184	T	TCC	S
2205	T	GGA	G
2694	A	GTT	V
2697	T	ACC	T
3318	T	GGA	G
3324	T	TTC	F
3591	G	AAA	K
3594	G	GTT	V
3597	G	GAC	D
4041	G	CAA	Q
4044	G	GTT	V
4047	T	AAC	N
4137	C	TCT	S
4143	T	TAC	Y
4218	G	AAA	K
4224	T	TTC	F
4254	G	GTC	V

FIG. 4B

NC-Splice Acceptor Changes

Location in Bayer BDD-Factor VIII cDNA	Nucleotide change	Codon	Amino Acid
154	A → C	CGC	R
156	A → C	CGC	R
288	G → A	CAA	Q
346	A → T	TCC	S
347	G → C	TCC	S
348	T → C	TCC	S
711	G → A	CAA	Q
1522	A → C	CGC	R
1524	G → C	CGC	R
1572	A → C	CCC	P
1851	A → C	CCC	P
2079	A → C	TCC	S
2343	G → A	CAA	Q
2574	T → A	GTA	V
2577	T → A	GTA	V
2610	G → A	CAA	Q
2737	A → T	TCC	S
2738	G → C	TCC	S
2742	T → C	CTC	L
2745	T → A	ATA	I
2748	T → A	TCA	S
3250	A → T	TCC	S
3251	G → C	TCC	S
3252	T → C	TCC	S
3315	A → C	CCC	P
3427	A → T	TCC	S
3428	G → C	TCC	S
3675	G → A	CAA	Q
4005	T → A	CTA	L
4011	T → A	CTA	L
4135	A → T	TCT	S
4136	G → C	TCC	S
4161	C → A	ATA	I
4164	C → G	TCG	S
4165	A → T	TCG	S
4166	G → C	TCG	S
4167	C → G	TCG	S
4168	A → T	TCG	S
4169	G → C	TCG	S
4170	T → G	TCG	S
4203	G → A	CAA	Q

000000 09225500

[illegible]

Location in Bayer BDD-Factor VIII cDNA

[illegible]

Position	Sequence	Sequence	Sequence
504	T	C	S
703	T	C	L
705	G	C	L
955	T	C	L
957	G	C	L
1110	T	C	T
1441	T	C	L
1443	G	C	L
1500	T	C	T
1668	T	C	V
1923	T	C	S
2406	T	C	S
2592	T	C	T
2892	T	C	S
2898	T	C	V
2955	T	C	T
3024	T	C	S
3696	T	C	L
3742	T	C	L
3744	A	C	L
3795	T	C	F
4281	G	C	L

[illegible]

		5	10	15	20	25	30	35	40	45						
		*	*	*	*	*	*	*	*	*						
pDJCcoding	ATG	GAA	ATA	GAG	CTC	TCC	ACC	TGC	TTC	TTT	CTG	TGC	CTT	TTG	CGA	TTC
1. p25Dcod				10			20			30				40		
[16902]	ATG	GAA	ATA	GAG	CTC	TCC	ACC	TGC	TTC	TTT	CTG	TGC	CTT	TTG	CGA	TTC>
	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^
pDJCcoding	ATG	GAA	ATA	GAG	CTC	TCC	ACC	TGC	TTC	TTT	CTG	TGC	CTT	TTG	CGA	TTC
		50	55	60	65	70	75	80	85	90	95					
		*	*	*	*	*	*	*	*	*	*					
pDJCcoding	TGC	TTT	AGT	GCC	ACC	AGA	AGA	TAC	TAC	CTG	GGT	GCA	GTG	GAA	CTG	TCA
1. p25Dcod				60			70			80				90		
[16902]	TGC	TTT	AGT	GCC	ACC	AGA	AGA	TAC	TAC	CTG	GGT	GCA	GTG	GAA	CTG	TCA>
	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^
pDJCcoding	TGC	TTT	AGT	GCC	ACC	AGA	AGA	TAC	TAC	CTG	GGT	GCA	GTG	GAA	CTG	TCA
		100	105	110	115	120	125	130	135	140						
		*	*	*	*	*	*	*	*	*						
pDJCcoding	TGG	GAC	TAT	ATG	CAA	AGT	GAT	CTC	GGA	GAG	CTG	CCT	GTG	GAC	GCA	AGA
1. p25Dcod		100			110			120			130			140		
[16902]	TGG	GAC	TAT	ATG	CAA	AGT	GAT	CTC	GGT	GAG	CTG	CCT	GTG	GAC	GCA	AGA>
	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^
pDJCcoding	TGG	GAC	TAT	ATG	CAA	AGT	GAT	CTC	GGA	GAG	CTG	CCT	GTG	GAC	GCA	AGA
		145	150	155	160	165	170	175	180	185	190					
		*	*	*	*	*	*	*	*	*	*					
pDJCcoding	TTT	OCT	OCT	OGC	GTG	CCA	AAA	TCT	TTT	CCA	TTC	AAC	ACC	TCA	GTC	GTG
1. p25Dcod		150			160			170			180			190		
[16902]	TTT	OCT	OCT	aGa	GTG	CCA	AAA	TCT	TTT	CCA	TTC	AAC	ACC	TCA	GTC	GTG>
	^^^	^^^	^^^	vvv	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^
pDJCcoding	TTT	OCT	OCT	OGC	GTG	CCA	AAA	TCT	TTT	CCA	TTC	AAC	ACC	TCA	GTC	GTG
		195	200	205	210	215	220	225	230	235	240					
		*	*	*	*	*	*	*	*	*	*					
pDJCcoding	TAC	AAA	AAG	ACT	CTG	TTT	GTA	GAA	TTC	ACG	GTT	CAC	CTT	TTC	AAC	ATC
1. p25Dcod			200			210			220			230			240	
[16902]	TAC	AAA	AAG	ACT	CTG	TTT	GTA	GAA								

[illegible]

	290	295	300	305	310	315	320	325	330	335						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	GCT	GAG	GTT	TAT	GAT	ACA	GTG	GTC	ATT	ACA	CTT	AAG	AAC	ATG	GCT	TCC
1. p25Dco290				300			310				320			330		
[16902]	GCT	GAG	GTT	TAT	GAT	ACA	GTG	GTC	ATT	ACA	CTT	AAG	AAC	ATG	GCT	TCC>
	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^
pDJCcoding	GCT	GAG	GTT	TAT	GAT	ACA	GTG	GTC	ATT	ACA	CTT	AAG	AAC	ATG	GCT	TCC

	340	345	350	355	360	365	370	375	380							
	*	*	*	*	*	*	*	*	*							
pDJCcoding	CAT	CCT	GTC	TCC	CTT	CAT	GCT	GTT	GGT	GTA	TCC	TAC	TGG	AAA	GCT	TCT
1. p25Dcod	340				350			360				370			380	
[16902]	CAT	CCT	GTC	agt	CTT	CAT	GCT	GTT	GGT	GTA	TCC	TAC	TGG	AAA	GCT	TCT>
	aaa	aaa	aaa	vvv	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa
pDJCcoding	CAT	CCT	GTC	TCC	CTT	CAT	GCT	GTT	GGT	GTA	TCC	TAC	TGG	AAA	GCT	TCT

	385	390	395	400	405	410	415	420	425	430						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	GAG	GGA	GCT	GAA	TAT	GAT	GAT	CAG	ACC	AGT	CAA	AGG	GAG	AAA	GAA	GAT
1. p25Dcod		390			400			410				420				430
[16902]	GAG	GGA	GCT	GAA	TAT	GAT	GAT	CAG	ACC	AGT	CAA	AGG	GAG	AAA	GAA	GAT>
	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^
pDJCcoding	GAG	GGA	GCT	GAA	TAT	GAT	GAT	CAG	ACC	AGT	CAA	AGG	GAG	AAA	GAA	GAT

	435	440	445	450	455	460	465	470	475	480						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	GAT	AAA	GTC	TTC	OCT	GGT	GGA	AGC	CAT	ACA	TAT	GTC	TGG	CAA	GTC	CTG
1. p25Dcod		440			450		460			470						480
[16902]	GAT	AAA	GTC	TTC	OCT	GGT	GGA	AGC	CAT	ACA	TAT	GTC	TGG	CAG	GTC	CTG>
	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA
pDJCcoding	GAT	AAA	GTC	TTC	OCT	GGT	GGA	AGC	CAT	ACA	TAT	GTC	TGG	CAA	GTC	CTG

		485	490	495	500	505	510	515	520	525						
		*	*	*	*	*	*	*	*	*						
pDJCcoding	AAA	GAG	AAT	GGT	CCA	ATG	GCC	TCC	GAC	CCA	CTG	TGC	CTT	ACC	TAC	TCA
1. p25Dcod			490		500		510		520							
[16902]	AAA	GAG	AAT	GGT	CCA	ATG	GCC	TCT	GAC	CCA	CTG	TGC	CTT	ACC	TAC	TCA>
	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA
pDJCcoding	AAA	GAG	AAT	GGT	CCA	ATG	GCC	TCC	GAC	CCA	CTG	TGC	CTT	ACC	TAC	TCA

530 535 540 545 550 555 560 565 570 575
★ ★ ★ ★ ★ ★ ★ ★ ★ ★

[illegible]

	1. p25Dco530		540		550		560		570							
(16902]	TAT	CTT	TCT	CAT	GTG	GAC	CTG	GTA	AAA	GAC	TTG	AAT	TCA	GGC	CTC	ATT>
	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^
pDJCcoding	TAT	CTT	TCT	CAT	GTG	GAC	CTG	GTT	AAA	GAC	TTG	AAT	TCA	GGC	CTC	ATT

	580	585	590	595	600	605	610	615	620							
	*	*	*	*	*	*	*	*	*							
pDJCcoding	GGA	GCC	CTA	CTA	GTA	TGT	AGA	GAA	GGG	AGT	CTG	GCC	AAG	GAA	AAG	ACA
1. p25Dcod	580				590			600				610				620
[16902]	GGA	GCC	CTA	CTA	GTA	TGT	AGA	GAA	GGG	AGT	CTG	GCC	AAG	GAA	AAG	ACA>
	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^
pDJCcoding	GGA	GCC	CTA	CTA	GTA	TGT	AGA	GAA	GGG	AGT	CTG	GCC	AAG	GAA	AAG	ACA

	625	630	635	640	645	650	655	660	665	670						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	CAG	ACC	TTG	CAC	AAA	TTT	ATA	CTA	CTT	TTT	GCT	GTA	TTT	GAT	GAA	GGG
1. p25Dcod		630			640			650				660				670
[16902]	CAG	ACC	TTG	CAC	AAA	TTT	ATA	CTA	CTT	TTT	GCT	GTA	TTT	GAT	GAA	GGG>
	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^
pDJCcoding	CAG	ACC	TTG	CAC	AAA	TTT	ATA	CTA	CTT	TTT	GCT	GTA	TTT	GAT	GAA	GGG

	675	680	685	690	695	700	705	710	715	720
	*	*	*	*	*	*	*	*	*	*
pDJCcoding	AAA	AGT TGG	CAC TCA	GAA ACA	AAG AAC	TCC CTC	ATG CAA	GAT AGG	GAT	
1. p25Dcod		680		690		700		710		720
[16902]	AAA	AGT TGG	CAC TCA	GAA ACA	AAG AAC	TCC CTC	ATG CAA	GAT AGG	GAT	
	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA
pDJCcoding	AAA	AGT TGG	CAC TCA	GAA ACA	AAG AAC	TCC CTC	ATG CAA	GAT AGG	GAT	

		725	730	735	740	745	750	755	760	765						
		*	*	*	*	*	*	*	*	*						
pDJCcoding	GCT	GCA	TCT	GCT	CGG	GCC	TGG	CCT	AAA	ATG	CAC	ACA	GTC	AAT	GGT	TAT
1. p25Dcod			730			740			750				760			
[16902]	GCT	GCA	TCT	GCT	CGG	GCC	TGG	CCT	AAA	ATG	CAC	ACA	GTC	AAT	GGT	TAT>
	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA
pDJCcoding	GCT	GCA	TCT	GCT	CGG	GCC	TGG	CCT	AAA	ATG	CAC	ACA	GTC	AAT	GGT	TAT

	770	775	780	785	790	795	800	805	810	815						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	GTA	AAC	AGG	AGC	CTG	CCA	GGA	CTG	ATT	GGA	TGC	CAC	AGG	AAA	TCA	GTC
1. p25Dco770			780			790		800		810						
[16902]	GTA	AAC	AGG	tct	CTG	CCA	GGT	CTG	ATT	GGA	TGC	CAC	AGG	AAA	TCA	GTC→
	AAA	AAA	AAA	vvv	AAA	AAA	AAv	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA
pDJCcoding	GTA	AAC	AGG	AGC	CTG	CCA	GGA	CTG	ATT	GGA	TGC	CAC	AGG	AAA	TCA	GTC

820 825 830 835 840 845 850 855 860
* * * * *
pDJCoding TAT TGG CAT GTT ATA GGA ATG GGC ACC ACT CCT GAA GTG CAC TCA ATA

[illegible]

	1155	1160	1165	1170	1175	1180	1185	1190	1195	1200						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	CCT	TCC	TTT	ATC	CAA	ATT	CGC	TCA	GTT	GCC	AAG	AAG	CAT	CCT	AAA	ACT
1. p25Dcod		1160			1170			1180				1190				1200
[16902]	CCT	TCC	TTT	ATC	CAA	ATT	CGC	TCA	GTT	GCC	AAG	AAG	CAT	CCT	AAA	ACT>
	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^
pDJCcoding	CCT	TCC	TTT	ATC	CAA	ATT	CGC	TCA	GTT	GCC	AAG	AAG	CAT	CCT	AAA	ACT

		1205	1210	1215	1220	1225	1230	1235	1240	1245						
		*	*	*	*	*	*	*	*	*						
pDJCcoding	TGG	GTA	CAT	TAC	ATT	GCT	GCT	GAA	GAG	GAG	GAC	TGG	GAC	TAT	GCT	CCC
1. p25Dcod			1210			1220			1230				1240			
[16902]	TGG	GTA	CAT	TAC	ATT	GCT	GCT	GAA	GAG	GAG	GAC	TGG	GAC	TAT	GCT	CCC>
	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^
pDJCcoding	TGG	GTA	CAT	TAC	ATT	GCT	GCT	GAA	GAG	GAG	GAC	TGG	GAC	TAT	GCT	CCC

	1250	1255	1260	1265	1270	1275	1280	1285	1290	1295						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	TTA	GTC	CTC	GCC	CCC	GAT	GAC	AGA	AGT	TAT	AAA	AGT	CAA	TAT	TTG	AAC
1. p25Dc1250				1260			1270			1280				1290		
[16902]	TTA	GTC	CTC	GCC	CCC	GAT	GAC	AGA	AGT	TAT	AAA	AGT	CAA	TAT	TTG	AAC>
	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^
pDJCcoding	TTA	GTC	CTC	GCC	CCC	GAT	GAC	AGA	AGT	TAT	AAA	AGT	CAA	TAT	TTG	AAC

	1300	1305	1310	1315	1320	1325	1330	1335	1340
	*	*	*	*	*	*	*	*	*
pDJCcoding	AAT GGC OCT CAG CGG ATT GGA AGG AAG TAC AAA AAA GTC CGA TTT ATG								
1. p25Dcod	1300		1310		1320		1330		1340
[16902]	AAT GGC OCT CAG CGG ATT GGT AGG AAG TAC AAA AAA GTC CGA TTT ATG>								
	***	***	***	***	***	***	***	***	***
pDJCcoding	AAT GGC OCT CAG CGG ATT GGA AGG AAG TAC AAA AAA GTC CGA TTT ATG								

	1345	1350	1355	1360	1365	1370	1375	1380	1385	1390						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	GCA	TAC	ACA	GAT	GAA	ACC	TTT	AAG	ACT	CGT	GAA	GCT	ATT	CAG	CAT	GAA
1. p25Dcod		1350			1360			1370			1380					1390
[16902]	GCA	TAC	ACA	GAT	GAA	ACC	TTT	AAG	ACT	CGT	GAA	GCT	ATT	CAG	CAT	GAA>
	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^
pDJCcoding	GCA	TAC	ACA	GAT	GAA	ACC	TTT	AAG	ACT	CGT	GAA	GCT	ATT	CAG	CAT	GAA

	1395	1400	1405	1410	1415	1420	1425	1430	1435	1440
	*	*	*	*	*	*	*	*	*	*
pDJCcoding	TCA	GGA ATC	TTG GGA	CCT TTA	CTT TAT	GGG GAA	GTT GGA	GAC ACA	CTG	
1. p25Dcod		1400		1410		1420		1430		1440
[16902]	TCA	GGA ATC	TTG GGA	CCT TTA	CTT TAT	GGG GAA	GTT GGA	GAC ACA	CTG>	
	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^
pDJCcoding	TCA	GGA ATC	TTG GGA	CCT TTA	CTT TAT	GGG GAA	GTT GGA	GAC ACA	CTG	

FIG. 5F

	1445	1450	1455	1460	1465	1470	1475	1480	1485							
	*	*	*	*	*	*	*	*	*							
pDJCcoding	CTC	ATT	ATA	TTT	AAG	AAT	CAA	GCA	AGC	AGA	CCA	TAT	AAC	ATC	TAC	CCT
1. p25Dcod		1450		1460		1470		1480								
(16902]	tTg	ATT	ATA	TTT	AAG	AAT	CAA	GCA	AGC	AGA	CCA	TAT	AAC	ATC	TAC	CCT>
	v^v	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa
pDJCcoding	CTC	ATT	ATA	TTT	AAG	AAT	CAA	GCA	AGC	AGA	CCA	TAT	AAC	ATC	TAC	CCT

	1490	1495	1500	1505	1510	1515	1520	1525	1530	1535						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	CAC	GGA	ATC	ACC	GAT	GTC	CGT	CCT	TTG	TAT	TCA	CGC	AGA	TTA	CCA	AAA
1. p25Dc1490		1500		1510		1520		1530								
(16902]	CAC	GGA	ATC	ACt	GAT	GTC	CGT	CCT	TTG	TAT	TCA	aGg	AGA	TTA	CCA	AAA>
	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	v^v	aaa	aaa	aaa	aaa
pDJCcoding	CAC	GGA	ATC	ACC	GAT	GTC	CGT	CCT	TTG	TAT	TCA	CGC	AGA	TTA	CCA	AAA

	1540	1545	1550	1555	1560	1565	1570	1575	1580							
	*	*	*	*	*	*	*	*	*							
pDJCcoding	GGA	GTA	AAA	CAT	TTG	AAG	GAT	TTT	CCA	ATT	CTG	CCC	GGA	GAA	ATA	TTC
1. p25Dcod	1540		1550		1560		1570		1580							
(16902]	GGt	GTA	AAA	CAT	TTG	AAG	GAT	TTT	CCA	ATT	CTG	CCa	GGA	GAA	ATA	TTC>
	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa
pDJCcoding	GGA	GTA	AAA	CAT	TTG	AAG	GAT	TTT	CCA	ATT	CTG	CCC	GGA	GAA	ATA	TTC

	1585	1590	1595	1600	1605	1610	1615	1620	1625	1630						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	AAA	TAT	AAA	TGG	ACA	GTG	ACT	GTA	GAA	GAT	GGG	CCA	ACT	AAA	TCA	GAT
1. p25Dcod	1590		1600		1610		1620		1630							
(16902]	AAA	TAT	AAA	TGG	ACA	GTG	ACT	GTA	GAA	GAT	GGG	CCA	ACT	AAA	TCA	GAT>
	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa
pDJCcoding	AAA	TAT	AAA	TGG	ACA	GTG	ACT	GTA	GAA	GAT	GGG	CCA	ACT	AAA	TCA	GAT

	1635	1640	1645	1650	1655	1660	1665	1670	1675	1680						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	CCT	CGG	TGC	CTG	ACC	CGC	TAT	TAC	TCT	AGT	TTC	GTC	AAT	ATG	GAG	AGA
1. p25Dcod	1640		1650		1660		1670		1680							
(16902]	CCT	CGG	TGC	CTG	ACC	CGC	TAT	TAC	TCT	AGT	TTC	GTC	AAT	ATG	GAG	AGA>
	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa
pDJCcoding	CCT	CGG	TGC	CTG	ACC	CGC	TAT	TAC	TCT	AGT	TTC	GTC	AAT	ATG	GAG	AGA

	1685	1690	1695	1700	1705	1710	1715	1720	1725							
	*	*	*	*	*	*	*	*	*							
pDJCcoding	GAT	CTA	GCT	TCA	GGA	CTC	ATT	GGC	CCT	CTC	CTC	ATC	TGC	TAC	AAA	GAA
1. p25Dcod	1690		1700		1710		1720									
(16902]	GAT	CTA	GCT	TCA	GGA	CTC	ATT	GGC	CCT	CTC	CTC	ATC	TGC	TAC	AAA	GAA>
	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa	aaa
pDJCcoding	GAT	CTA	GCT	TCA	GGA	CTC	ATT	GGC	CCT	CTC	CTC	ATC	TGC	TAC	AAA	GAA

000210-09225900

FIG. 56

	1730	1735	1740	1745	1750	1755	1760	1765	1770	1775						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	TCT	GTA	GAT	CAA	AGA	GGA	AAC	CAG	ATA	ATG	TCA	GAC	AAG	AGG	AAT	GTC
1. p25Dc1730			1740			1750		1760		1770						
[16902]	TCT	GTA	GAT	CAA	AGA	GGA	AAC	CAG	ATA	ATG	TCA	GAC	AAG	AGG	AAT	GTC>
	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^
pDJCcoding	TCT	GTA	GAT	CAA	AGA	GGA	AAC	CAG	ATA	ATG	TCA	GAC	AAG	AGG	AAT	GTC

	1780	1785	1790	1795	1800	1805	1810	1815	1820							
	*	*	*	*	*	*	*	*	*							
pDJCcoding	ATC	CTG	TTT	TCT	GTA	TTT	GAT	GAG	AAC	CGA	AGC	TGG	TAC	CTC	ACA	GAG
1. p25Dcod 1780			1790		1800		1810		1820							
[16902]	ATC	CTG	TTT	TCT	GTA	TTT	GAT	GAG	AAC	CGA	AGC	TGG	TAC	CTC	ACA	GAG>
	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^
pDJCcoding	ATC	CTG	TTT	TCT	GTA	TTT	GAT	GAG	AAC	CGA	AGC	TGG	TAC	CTC	ACA	GAG

	1825	1830	1835	1840	1845	1850	1855	1860	1865	1870						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	AAT	ATA	CAA	CGC	TTT	CTC	CCC	AAT	CCC	GCT	GGA	GTG	CAG	CTT	GAG	GAT
1. p25Dcod 1830			1840		1850		1860		1870							
[16902]	AAT	ATA	CAA	CGC	TTT	CTC	CCC	AAT	CCa	GCT	GGA	GTG	CAG	CTT	GAG	GAT>
	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^
pDJCcoding	AAT	ATA	CAA	CGC	TTT	CTC	CCC	AAT	CCC	GCT	GGA	GTG	CAG	CTT	GAG	GAT

	1875	1880	1885	1890	1895	1900	1905	1910	1915	1920						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	CCA	GAG	TTC	CAA	GCC	TCC	AAC	ATC	ATG	CAC	AGC	ATC	AAT	GGC	TAT	GTT
1. p25Dcod 1880			1890		1900		1910		1920							
[16902]	CCA	GAG	TTC	CAA	GCC	TCC	AAC	ATC	ATG	CAC	AGC	ATC	AAT	GGC	TAT	GTT>
	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^
pDJCcoding	CCA	GAG	TTC	CAA	GCC	TCC	AAC	ATC	ATG	CAC	AGC	ATC	AAT	GGC	TAT	GTT

	1925	1930	1935	1940	1945	1950	1955	1960	1965							
	*	*	*	*	*	*	*	*	*							
pDJCcoding	TTC	GAT	AGT	TTG	CAG	TTG	TCA	GTT	TGT	TTG	CAT	GAA	GTA	GCA	TAC	TGG
1. p25Dcod 1930			1940		1950		1960									
[16902]	TTC	GAT	AGT	TTG	CAG	TTG	TCA	GTT	TGT	TTG	CAT	GAG	GTg	GCA	TAC	TGG>
	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^
pDJCcoding	TTC	GAT	AGT	TTG	CAG	TTG	TCA	GTT	TGT	TTG	CAT	GAA	GTA	GCA	TAC	TGG

	1970	1975	1980	1985	1990	1995	2000	2005	2010	2015						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	TAC	ATT	CTA	AGC	ATT	GGA	GCA	CAG	ACT	GAC	TTC	CTT	TCT	GTC	TTC	TTC
1. p25Dc1970			1980		1990		2000		2010							
[16902]	TAC	ATT	CTA	AGC	ATT	GGA	GCA	CAG	ACT	GAC	TTC	CTT	TCT	GTC	TTC	TTC>
	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^
pDJCcoding	TAC	ATT	CTA	AGC	ATT	GGA	GCA	CAG	ACT	GAC	TTC	CTT	TCT	GTC	TTC	TTC

2020	2025	2030	2035	2040	2045	2050	2055	2060
*	*	*	*	*	*	*	*	*

00000-09225560

[illegible]

2595 2600 2605 2610 2615 2620 2625 2630 2635 2640
 * * * * * * * *
 pDJCcoding GAT GGC TCC TTT ACT CAA CCC TTA TAC CGT GGA GAA CTA AAT GAA CAT
 | | |
 1. p25Dcod 2600 2610 2620 2630 2640
 [16902] GAT GGC TCC TTT ACT CAG CCC TTA TAC CGT GGA GAA CTA AAT GAA CAT>

FIG. 5J

^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^
 pDJCcoding GAT GGC TCC TTT ACT CAA CCC TTA TAC CGT GGA GAA CTA AAT GAA CAT

2645 2650 2655 2660 2665 2670 2675 2680 2685
 * * * * *
 pDJCcoding TTG GGA CTC CTG GGG CCA TAT ATA AGA GCA GAA GTT GAA GAT AAT ATC

1. p25Dcod 2650 2660 2670 2680
 [16902] TTG GGA CTC CTG GGG CCA TAT ATA AGA GCA GAA GTT GAA GAT AAT ATC>
 ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^
 pDJCcoding TTG GGA CTC CTG GGG CCA TAT ATA AGA GCA GAA GTT GAA GAT AAT ATC

2690 2695 2700 2705 2710 2715 2720 2725 2730 2735
 * * * * *
 pDJCcoding ATG GTT ACC TTC AGA AAT CAG GCC TCT CGT CCC TAT TCC TTC TAT TCT

1. p25Dcod 2690 2700 2710 2720 2730
 [16902] ATG GTT ACC TTC AGA AAT CAG GCC TCT CGT CCC TAT TCC TTC TAT TCT>
 ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^
 pDJCcoding ATG GTT ACC TTC AGA AAT CAG GCC TCT CGT CCC TAT TCC TTC TAT TCT

2740 2745 2750 2755 2760 2765 2770 2775 2780
 * * * * *
 pDJCcoding TCC CTC ATA TCA TAT GAG GAA GAT CAG AGG CAA GGA GCA GAA CCT AGA

1. p25Dcod 2740 2750 2760 2770 2780
 [16902] agC CTt ATt Tct TAT GAG GAA GAT CAG AGG CAA GGA GCA GAA CCT AGA>
 vv^ ^v^ ^v^ ^v^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^
 pDJCcoding TCC CTC ATA TCA TAT GAG GAA GAT CAG AGG CAA GGA GCA GAA CCT AGA

2785 2790 2795 2800 2805 2810 2815 2820 2825 2830
 * * * * *
 pDJCcoding AAA AAC TTT GTC AAG CCT AAT GAA ACC AAA ACT TAC TTT TGG AAA GTG

1. p25Dcod 2790 2800 2810 2820 2830
 [16902] AAA AAC TTT GTC AAG CCT AAT GAA ACC AAA ACT TAC TTT TGG AAA GTG>
 ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^
 pDJCcoding AAA AAC TTT GTC AAG CCT AAT GAA ACC AAA ACT TAC TTT TGG AAA GTG

2835 2840 2845 2850 2855 2860 2865 2870 2875 2880
 * * * * *
 pDJCcoding CAA CAT CAT ATG GCA CCC ACT AAA GAT GAG TTT GAC TGC AAA GCC TGG

1. p25Dcod 2840 2850 2860 2870 2880
 [16902] CAA CAT CAT ATG GCA CCC ACT AAA GAT GAG TTT GAC TGC AAA GCC TGG>
 ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^
 pDJCcoding CAA CAT CAT ATG GCA CCC ACT AAA GAT GAG TTT GAC TGC AAA GCC TGG

2885 2890 2895 2900 2905 2910 2915 2920 2925
 * * * * *
 pDJCcoding GCT TAT TTC TCC GAT GTC GAC CTG GAA AAA GAT GTG CAC TCA GGC CTG

1. p25Dcod 2890 2900 2910 2920
 [16902] GCT TAT TTC Tct GAT GtT GAC CTG GAA AAA GAT GTG CAC TCA GGC CTG>
 ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^
 pDJCcoding GCT TAT TTC TCC GAT GTC GAC CTG GAA AAA GAT GTG CAC TCA GGC CTG

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FIG. 5K

	2930	2935	2940	2945	2950	2955	2960	2965	2970	2975						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	ATT	GGA	CCC	CTT	CTG	GTC	TGC	CAC	ACC	AAC	ACA	CTG	AAC	CCT	GCT	CAT
1. p25Dc	2930		2940		2950		2960		2970							
[16902]	ATT	GGA	CCC	CTT	CTG	GTC	TGC	CAC	ACC	AAC	ACA	CTG	AAC	CCT	GCT	CAT>
	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA
pDJCcoding	ATT	GGA	CCC	CTT	CTG	GTC	TGC	CAC	ACC	AAC	ACA	CTG	AAC	CCT	GCT	CAT

	2980	2985	2990	2995	3000	3005	3010	3015	3020							
	*	*	*	*	*	*	*	*	*							
pDJCcoding	GGG	AGA	CAA	GTG	ACA	GTA	CAG	GAA	TTT	GCT	CTG	TTT	TTC	ACC	ATC	TTC
1. p25Dcod	2980		2990		3000		3010		3020							
[16902]	GGG	AGA	CAA	GTG	ACA	GTA	CAG	GAA	TTT	GCT	CTG	TTT	TTC	ACC	ATC	TTT>
	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA
pDJCcoding	GGG	AGA	CAA	GTG	ACA	GTA	CAG	GAA	TTT	GCT	CTG	TTT	TTC	ACC	ATC	TTC

	3025	3030	3035	3040	3045	3050	3055	3060	3065	3070						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	GAT	GAG	ACC	AAA	AGC	TGG	TAC	TTC	ACT	GAA	AAT	ATG	GAA	AGA	AAC	TGC
1. p25Dcod	3030		3040		3050		3060		3070							
[16902]	GAT	GAG	ACC	AAA	AGC	TGG	TAC	TTC	ACT	GAA	AAT	ATG	GAA	AGA	AAC	TGC>
	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA
pDJCcoding	GAT	GAG	ACC	AAA	AGC	TGG	TAC	TTC	ACT	GAA	AAT	ATG	GAA	AGA	AAC	TGC

	3075	3080	3085	3090	3095	3100	3105	3110	3115	3120						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	AGG	GCT	CCC	TGC	AAT	ATC	CAG	ATG	GAA	GAT	CCC	ACT	TTT	AAA	GAG	AAT
1. p25Dcod	3080		3090		3100		3110		3120							
[16902]	AGG	GCT	CCC	TGC	AAT	ATC	CAG	ATG	GAA	GAT	CCC	ACT	TTT	AAA	GAG	AAT>
	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA
pDJCcoding	AGG	GCT	CCC	TGC	AAT	ATC	CAG	ATG	GAA	GAT	CCC	ACT	TTT	AAA	GAG	AAT

	3125	3130	3135	3140	3145	3150	3155	3160	3165							
	*	*	*	*	*	*	*	*	*							
pDJCcoding	TAT	CGC	TTC	CAT	GCA	ATC	AAT	GGC	TAC	ATA	ATG	GAT	ACA	CTA	CCT	GGC
1. p25Dcod	3130		3140		3150		3160									
[16902]	TAT	CGC	TTC	CAT	GCA	ATC	AAT	GGC	TAC	ATA	ATG	GAT	ACA	CTA	CCT	GGC>
	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA
pDJCcoding	TAT	CGC	TTC	CAT	GCA	ATC	AAT	GGC	TAC	ATA	ATG	GAT	ACA	CTA	CCT	GGC

	3170	3175	3180	3185	3190	3195	3200	3205	3210	3215						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	TTA	GTA	ATG	GCT	CAG	GAT	CAA	AGG	ATT	CGA	TGG	TAT	CTG	CTC	AGC	ATG
1. p25Dc	3170		3180		3190		3200		3210							
[16902]	TTA	GTA	ATG	GCT	CAG	GAT	CAA	AGG	ATT	CGA	TGG	TAT	CTG	CTC	AGC	ATG>
	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA	AAA
pDJCcoding	TTA	GTA	ATG	GCT	CAG	GAT	CAA	AGG	ATT	CGA	TGG	TAT	CTG	CTC	AGC	ATG

00000-092550

FIG. 5L

3220 3225 3230 3235 3240 3245 3250 3255 3260
 * * * * *
 pDJCcoding GGC AGC AAT GAA AAC ATC CAT TCT ATT CAT TTC TCC GGA CAT GTG TTC
 | | | | |
 1. p25Dcod 3220 3230 3240 3250 3260
 [16902] GGC AGC AAT GAA AAC ATC CAT TCT ATT CAT TTC agt GGA CAT GTG TTC>
 ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^
 pDJCcoding GGC AGC AAT GAA AAC ATC CAT TCT ATT CAT TTC TCC GGA CAT GTG TTC

3265 3270 3275 3280 3285 3290 3295 3300 3305 3310
 * * * * *
 pDJCcoding ACT GTA CGA AAA AAA GAG GAG TAT AAA ATG GCA CTG TAC AAT CTC TAT
 | | | | |
 1. p25Dcod 3270 3280 3290 3300 3310
 [16902] ACT GTA CGA AAA AAA GAG GAG TAT AAA ATG GCA CTG TAC AAT CTC TAT>
 ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^
 pDJCcoding ACT GTA CGA AAA AAA GAG GAG TAT AAA ATG GCA CTG TAC AAT CTC TAT

3315 3320 3325 3330 3335 3340 3345 3350 3355 3360
 * * * * *
 pDJCcoding CCC GGA GTT TTC GAG ACA GTG GAA ATG TTA CCA TCC AAA GCT GGA ATT
 | | | | |
 1. p25Dcod 3320 3330 3340 3350 3360
 [16902] CCa Ggt GTT Ttt GAG ACA GTG GAA ATG TTA CCA TCC AAA GCT GGA ATT>
 ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^
 pDJCcoding CCC GGA GTT TTC GAG ACA GTG GAA ATG TTA CCA TCC AAA GCT GGA ATT

3365 3370 3375 3380 3385 3390 3395 3400 3405
 * * * * *
 pDJCcoding TGG CGG GTG GAA TGC CTT ATT GGC GAG CAT CTA CAT GCT GGG ATG AGC
 | | | | |
 1. p25Dcod 3370 3380 3390 3400
 [16902] TGG CGG GTG GAA TGC CTT ATT GGC GAG CAT CTA CAT GCT GGG ATG AGC>
 ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^
 pDJCcoding TGG CGG GTG GAA TGC CTT ATT GGC GAG CAT CTA CAT GCT GGG ATG AGC

3410 3415 3420 3425 3430 3435 3440 3445 3450 3455
 * * * * *
 pDJCcoding ACA CTT TTT CTG GTG TAC TCC AAT AAG TGT CAG ACT CCC CTG GGA ATG
 | | | | |
 1. p25Dcod 3410 3420 3430 3440 3450
 [16902] ACA CTT TTT CTG GTG TAC agC AAT AAG TGT CAG ACT CCC CTG GGA ATG>
 ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^
 pDJCcoding ACA CTT TTT CTG GTG TAC TCC AAT AAG TGT CAG ACT CCC CTG GGA ATG

3460 3465 3470 3475 3480 3485 3490 3495 3500
 * * * * *
 pDJCcoding GCT TCT GGA CAC ATT AGA GAT TTT CAG ATT ACA GCT TCA GGA CAA TAT
 | | | | |
 1. p25Dcod 3460 3470 3480 3490 3500
 [16902] GCT TCT GGA CAC ATT AGA GAT TTT CAG ATT ACA GCT TCA GGA CAA TAT>
 ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^ ^^^
 pDJCcoding GCT TCT GGA CAC ATT AGA GAT TTT CAG ATT ACA GCT TCA GGA CAA TAT

3505 3510 3515 3520 3525 3530 3535 3540 3545 3550
 * * * * *

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FIG. 5M

pDJCcoding GGA CAG TGG GGC CCA AAG CTG GCC AGA CTT CAT TAT TCC GGA TCA ATC
 1. p25Dcod 3510 3520 3530 3540 3550
 [16902] GGA CAG TGG GGC CCA AAG CTG GCC AGA CTT CAT TAT TCC GGA TCA ATC>
 pDJCcoding GGA CAG TGG GGC CCA AAG CTG GCC AGA CTT CAT TAT TCC GGA TCA ATC
 3555 3560 3565 3570 3575 3580 3585 3590 3595 3600
 * * * * *
 pDJCcoding AAT GCC TGG AGC ACC AAG GAG CCC TTT TCT TGG ATC AAA GTT GAC CTG
 1. p25Dcod 3560 3570 3580 3590 3600
 [16902] AAT GCC TGG AGC ACC AAG GAG CCC TTT TCT TGG ATC AAG GTT GAT CTG>
 pDJCcoding AAT GCC TGG AGC ACC AAG GAG CCC TTT TCT TGG ATC AAA GTT GAC CTG
 3605 3610 3615 3620 3625 3630 3635 3640 3645
 * * * * *
 pDJCcoding TTG GCA CCA ATG ATT ATT CAC GGC ATC AAG ACC CAG GGT GCC CGT CAG
 1. p25Dcod 3610 3620 3630 3640
 [16902] TTG GCA CCA ATG ATT ATT CAC GGC ATC AAG ACC CAG GGT GCC CGT CAG>
 pDJCcoding TTG GCA CCA ATG ATT ATT CAC GGC ATC AAG ACC CAG GGT GCC CGT CAG
 3650 3655 3660 3665 3670 3675 3680 3685 3690 3695
 * * * * *
 pDJCcoding AAG TTC TCC AGC CTC TAC ATC TCT CAA TTT ATC ATC ATG TAT AGT CTC
 1. p25Dcod 3650 3660 3670 3680 3690
 [16902] AAG TTC TCC AGC CTC TAC ATC TCT CAA TTT ATC ATC ATG TAT AGT CTC>
 pDJCcoding AAG TTC TCC AGC CTC TAC ATC TCT CAA TTT ATC ATC ATG TAT AGT CTC
 3700 3705 3710 3715 3720 3725 3730 3735 3740
 * * * * *
 pDJCcoding GAT GGG AAG AAG TGG CAG ACT TAT CGA GGA AAT TCC ACT GGA ACC CTC
 1. p25Dcod 3700 3710 3720 3730 3740
 [16902] GAT GGG AAG AAG TGG CAG ACT TAT CGA GGA AAT TCC ACT GGA ACC CTC>
 pDJCcoding GAT GGG AAG AAG TGG CAG ACT TAT CGA GGA AAT TCC ACT GGA ACC CTC
 3745 3750 3755 3760 3765 3770 3775 3780 3785 3790
 * * * * *
 pDJCcoding ATG GTC TTC TTT GGC AAT GTG GAT TCA TCT GGG ATA AAA CAC AAT ATT
 1. p25Dcod 3750 3760 3770 3780 3790
 [16902] ATG GTC TTC TTT GGC AAT GTG GAT TCA TCT GGG ATA AAA CAC AAT ATT>
 pDJCcoding ATG GTC TTC TTT GGC AAT GTG GAT TCA TCT GGG ATA AAA CAC AAT ATT
 3795 3800 3805 3810 3815 3820 3825 3830 3835 3840
 * * * * *
 pDJCcoding TTC AAC CCT CCA ATT ATT GCT CGA TAC ATC CGT TTG CAC CCA ACT CAT
 | | | | |

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FIG. 5N

1. p25Dcod 3800 3810 3820 3830 3840
 (16902] TTT AAC CCT CCA ATT ATT GCT CGA TAC ATC CGT TTG CAC CCA ACT CAT>
 pDJCcoding TTC AAC CCT CCA ATT ATT GCT CGA TAC ATC CGT TTG CAC CCA ACT CAT

3845 3850 3855 3860 3865 3870 3875 3880 3885
 * * * * *
 pDJCcoding TAT AGC ATT CGC AGC ACT CTT CGC ATG GAG TTG ATG GGC TGT GAT TTA
 1. p25Dcod 3850 3860 3870 3880
 (16902] TAT AGC ATT CGC AGC ACT CTT CGC ATG GAG TTG ATG GGC TGT GAT TTA>
 pDJCcoding TAT AGC ATT CGC AGC ACT CTT CGC ATG GAG TTG ATG GGC TGT GAT TTA

3890 3895 3900 3905 3910 3915 3920 3925 3930 3935
 * * * * *
 pDJCcoding AAT AGT TGC AGC ATG CCA TTG GGA ATG GAG AGT AAA GCA ATA TCA GAT
 1. p25Dcod 3890 3900 3910 3920 3930
 (16902] AAT AGT TGC AGC ATG CCA TTG GGA ATG GAG AGT AAA GCA ATA TCA GAT>
 pDJCcoding AAT AGT TGC AGC ATG CCA TTG GGA ATG GAG AGT AAA GCA ATA TCA GAT

3940 3945 3950 3955 3960 3965 3970 3975 3980
 * * * * *
 pDJCcoding GCA CAG ATT ACT GCT TCA TCC TAC TTT ACC AAT ATG TTT GCC ACC TGG
 1. p25Dcod 3940 3950 3960 3970 3980
 (16902] GCA CAG ATT ACT GCT TCA TCC TAC TTT ACC AAT ATG TTT GCC ACC TGG>
 pDJCcoding GCA CAG ATT ACT GCT TCA TCC TAC TTT ACC AAT ATG TTT GCC ACC TGG

3985 3990 3995 4000 4005 4010 4015 4020 4025 4030
 * * * * *
 pDJCcoding TCT CCT TCA AAA GCT CGA CTA CAC CTA CAA GGG AGG AGT AAT GCC TGG
 1. p25Dcod 3990 4000 4010 4020 4030
 (16902] TCT CCT TCA AAA GCT CGA CTA CAC CTA CAA GGG AGG AGT AAT GCC TGG>
 pDJCcoding TCT CCT TCA AAA GCT CGA CTA CAC CTA CAA GGG AGG AGT AAT GCC TGG

4035 4040 4045 4050 4055 4060 4065 4070 4075 4080
 * * * * *
 pDJCcoding AGA CCT CAA GTT AAC AAT CCA AAA GAG TGG CTG CAA GTG GAC TTC CAG
 1. p25Dcod 4040 4050 4060 4070 4080
 (16902] AGA CCT CAG GTT AAT AAT CCA AAA GAG TGG CTG CAA GTG GAC TTC CAG>
 pDJCcoding AGA CCT CAA GTT AAC AAT CCA AAA GAG TGG CTG CAA GTG GAC TTC CAG

4085 4090 4095 4100 4105 4110 4115 4120 4125
 * * * * *
 pDJCcoding AAG ACA ATG AAA GTC ACA GGA GTA ACT ACT CAG GGA GTA AAA TCT CTG
 1. p25Dcod 4090 4100 4110 4120
 (16902] AAG ACA ATG AAA GTC ACA GGA GTA ACT ACT CAG GGA GTA AAA TCT CTG>

000270-090000

[illegible]

	4130	4135	4140	4145	4150	4155	4160	4165	4170	4175						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	CTT	ACC	TCT	ATG	TAC	GTG	AAG	GAG	TTC	CTC	ATA	TCG	TCG	TCG	CAA	GAT
1. p25Dc	4130			4140			4150			4160				4170		
[16902]	CTT	ACC	agc	ATG	Tat	GTG	AAG	GAG	TTC	CTC	ATc	TCc	agc	agt	CAA	GAT>
	^^^	^^^	vvv	^^^	^^v	^^^	^^^	^^^	^^^	^^^	^^v	^^v	vvv	vvv	^^^	^^^
pDJCcoding	CTT	ACC	TCT	ATG	TAC	GTG	AAG	GAG	TTC	CTC	ATA	TCG	TCG	TCG	CAA	GAT

	4180	4185	4190	4195	4200	4205	4210	4215	4220							
	*	*	*	*	*	*	*	*	*							
pDJCcoding	GGC	CAT	CAG	TGG	ACT	CTC	TTT	TTT	CAA	AAT	GGC	AAA	GTA	AAA	GTT	TTC
1. p25Dcod	4180			4190			4200				4210			4220		
[16902]	GGC	CAT	CAG	TGG	ACT	CTC	TTT	TTT	CAG	AAT	GGC	AAA	GTA	AAG	GTT	TTT>
	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^
pDJCcoding	GGC	CAT	CAG	TGG	ACT	CTC	TTT	TTT	CAA	AAT	GGC	AAA	GTA	AAA	GTT	TTC

	4225	4230	4235	4240	4245	4250	4255	4260	4265	4270						
	*	*	*	*	*	*	*	*	*	*						
pDJCcoding	CAG	GGA	AAT	CAA	GAC	TCC	TTC	ACA	CCT	GTC	GTG	AAC	TCT	CTA	GAC	CCA
1. p25Dcod	4230				4240			4250			4260				4270	
[16902]	CAG	GGA	AAT	CAA	GAC	TCC	TTC	ACA	CCT	GTg	GTG	AAC	TCT	CTA	GAC	CCA>
	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^
pDJCcoding	CAG	GGA	AAT	CAA	GAC	TCC	TTC	ACA	CCT	GTC	GTG	AAC	TCT	CTA	GAC	CCA

	4275	4280	4285	4290	4295	4300	4305	4310	4315	4320
	*	*	*	*	*	*	*	*	*	*
pDJCoding	CCG	TTA CTC	ACT CGC	TAC CTT	CGA ATT	CAC CCC	CAG AGT	TGG GTG	CAC	
1. p25Dcod		4280		4290		4300		4310		4320
[16902]	CCG	TTA CTC	ACT CGC	TAC CTT	CGA ATT	CAC CCC	CAG AGT	TGG GTG	CAC	
	^^	^^	^^	^^	^^	^^	^^	^^	^^	^^
pDJCoding	CCG	TTA CTC	ACT CGC	TAC CTT	CGA ATT	CAC CCC	CAG AGT	TGG GTG	CAC	

		4325	4330	4335	4340	4345	4350	4355	4360	4365	
		*	*	*	*	*	*	*	*	*	
pDJCcoding		CAG ATT GCC CTG AGG ATG GAG GTT CTG GGC TGC GAG GCA CAG GAC CTC									
1. p25Dcod		4330		4340		4350		4360			
[16902]		CAG ATT GCC CTG AGG ATG GAG GTT CTG GGC TGC GAG GCA CAG GAC CTC>									
		^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^	^^^
pDJCcoding		CAG ATT GCC CTG AGG ATG GAG GTT CTG GGC TGC GAG GCA CAG GAC CTC									

```

          4370
          *
pDJCcoding TAC TGA
          |
1. p25Do4370
[ 16902 ]   TAC TGA>
          ^   ^
pDJCcoding TAC TGA

```

FIG. 6

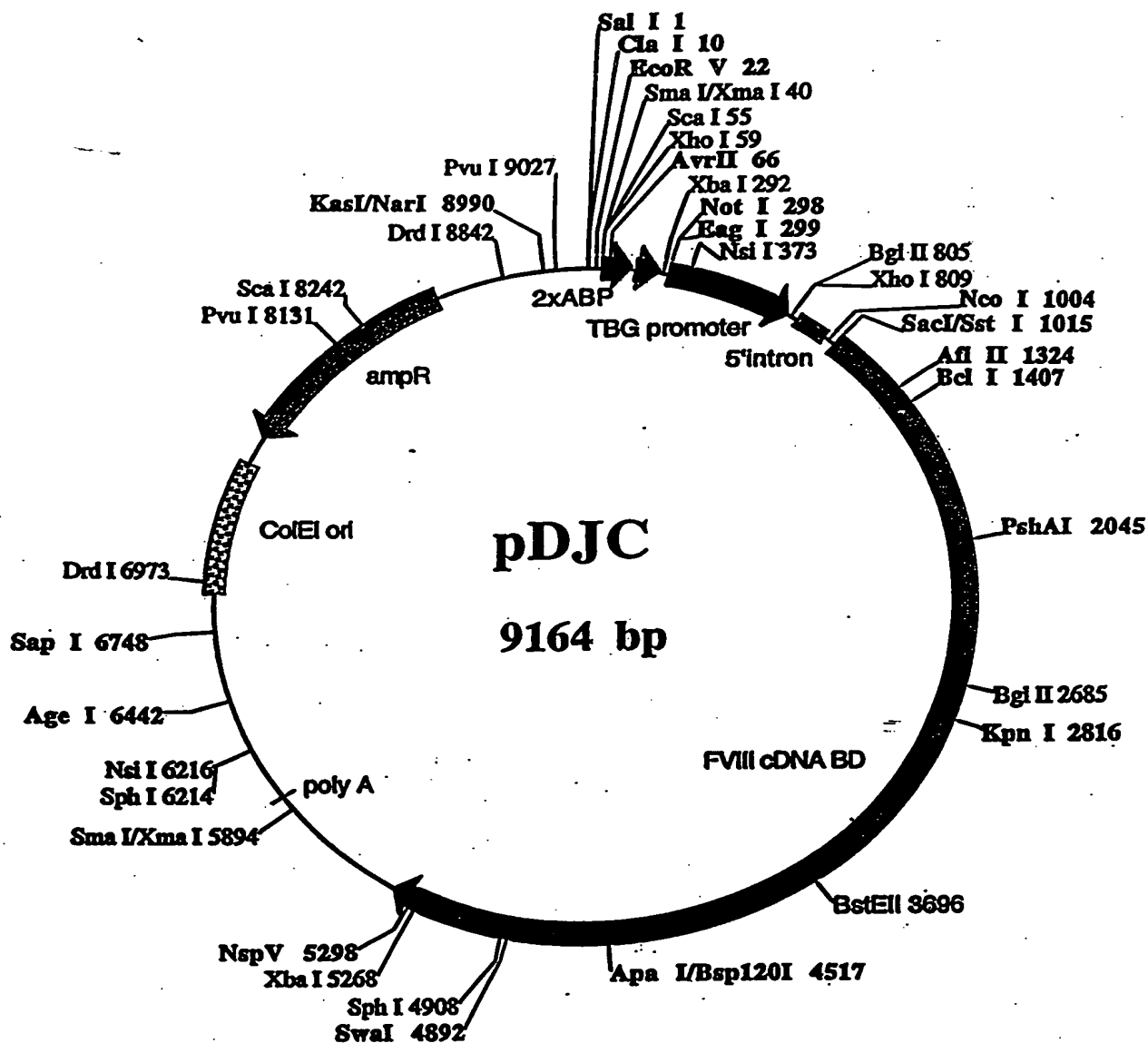
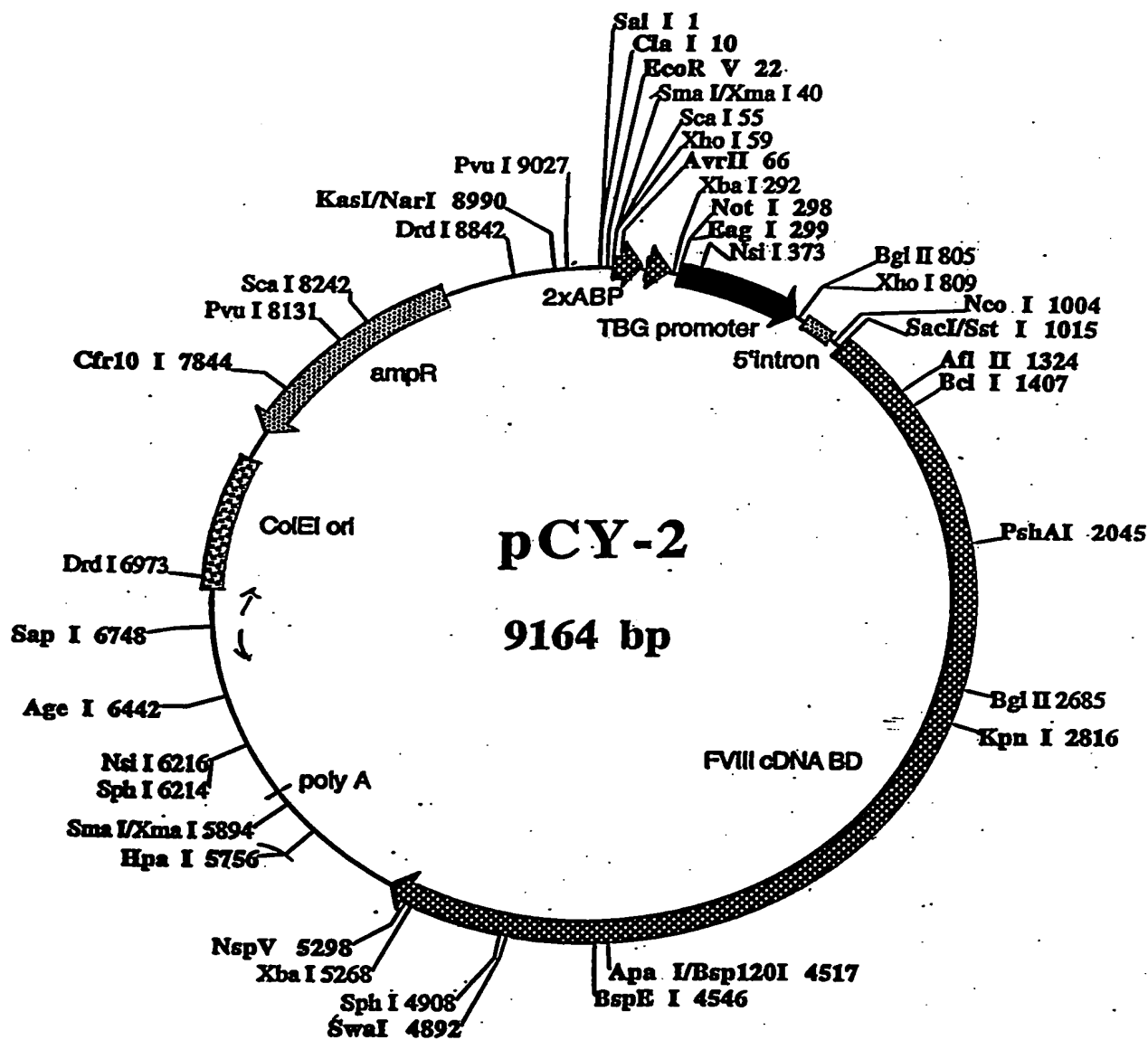


FIG. 7



000210-09225560

FIG. 8

Human Factor VIII cDNA Synthetic Approach

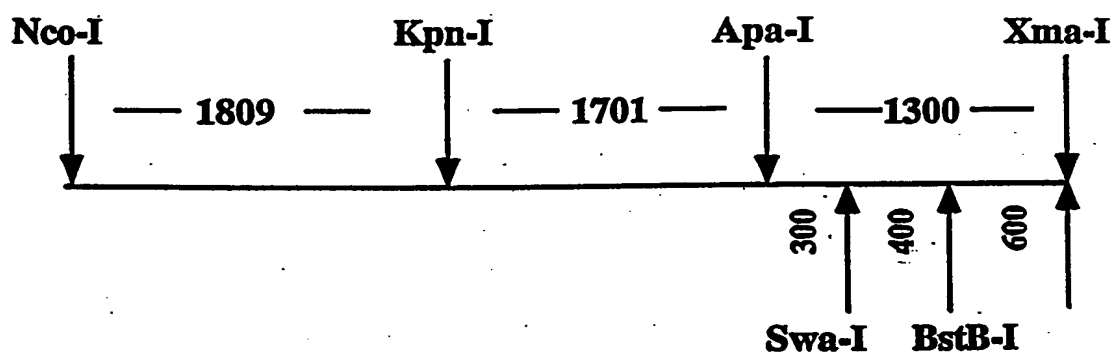
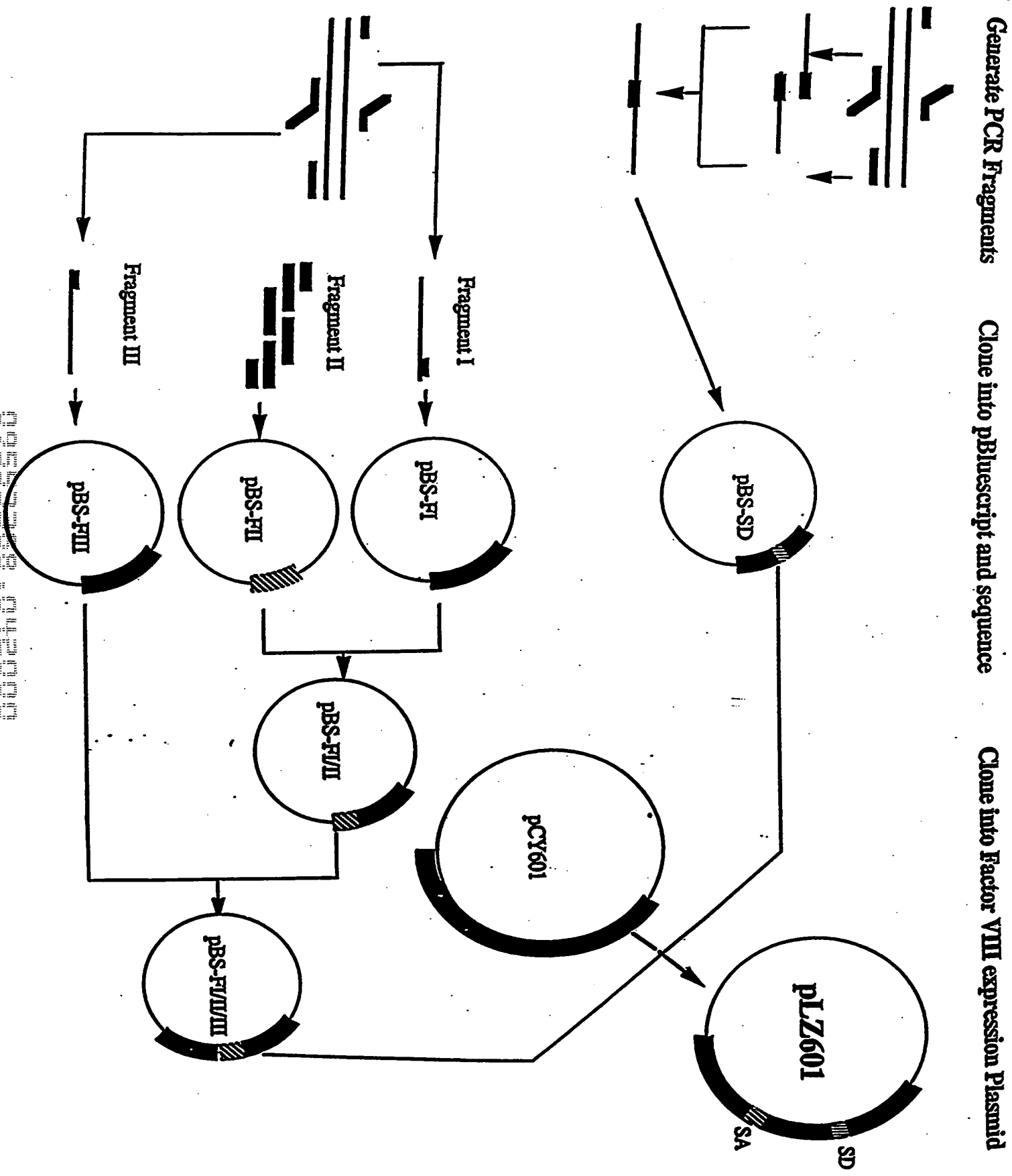


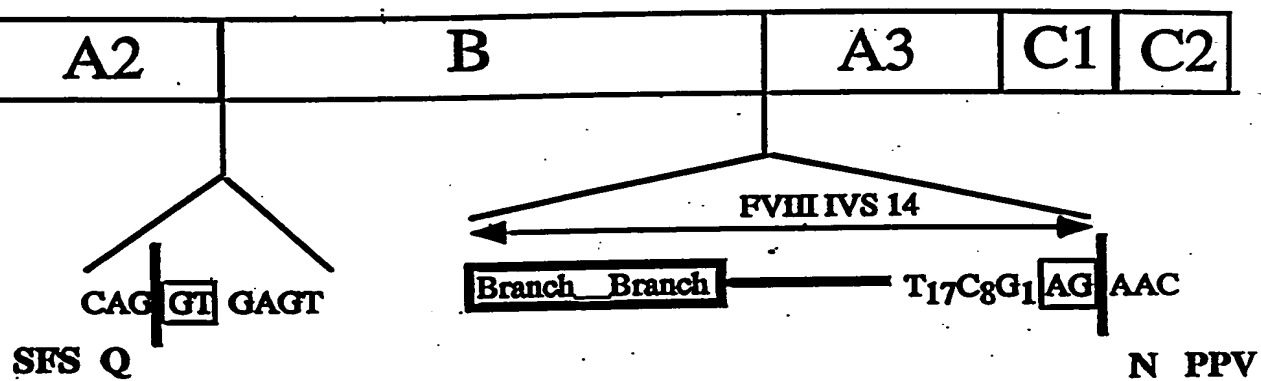
FIG. 9



09552222 042000

FIG. 10

Full-length Factor VIII cDNA



Factor VIII Full Length cDNA (Exon-Intron Boundary)

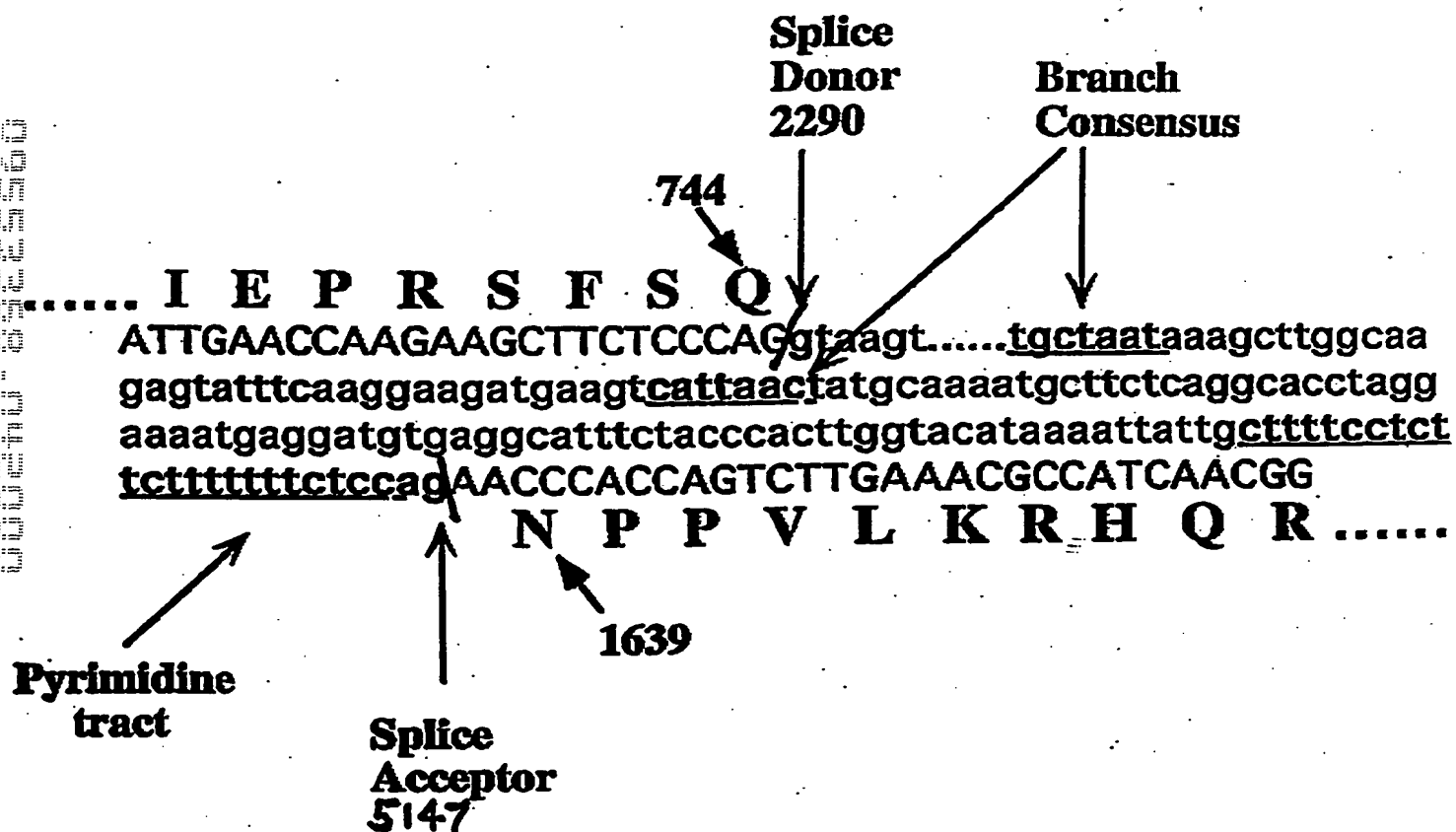


FIG. 12

Human Factor VIII cDNA: Intron Engineering Considerations

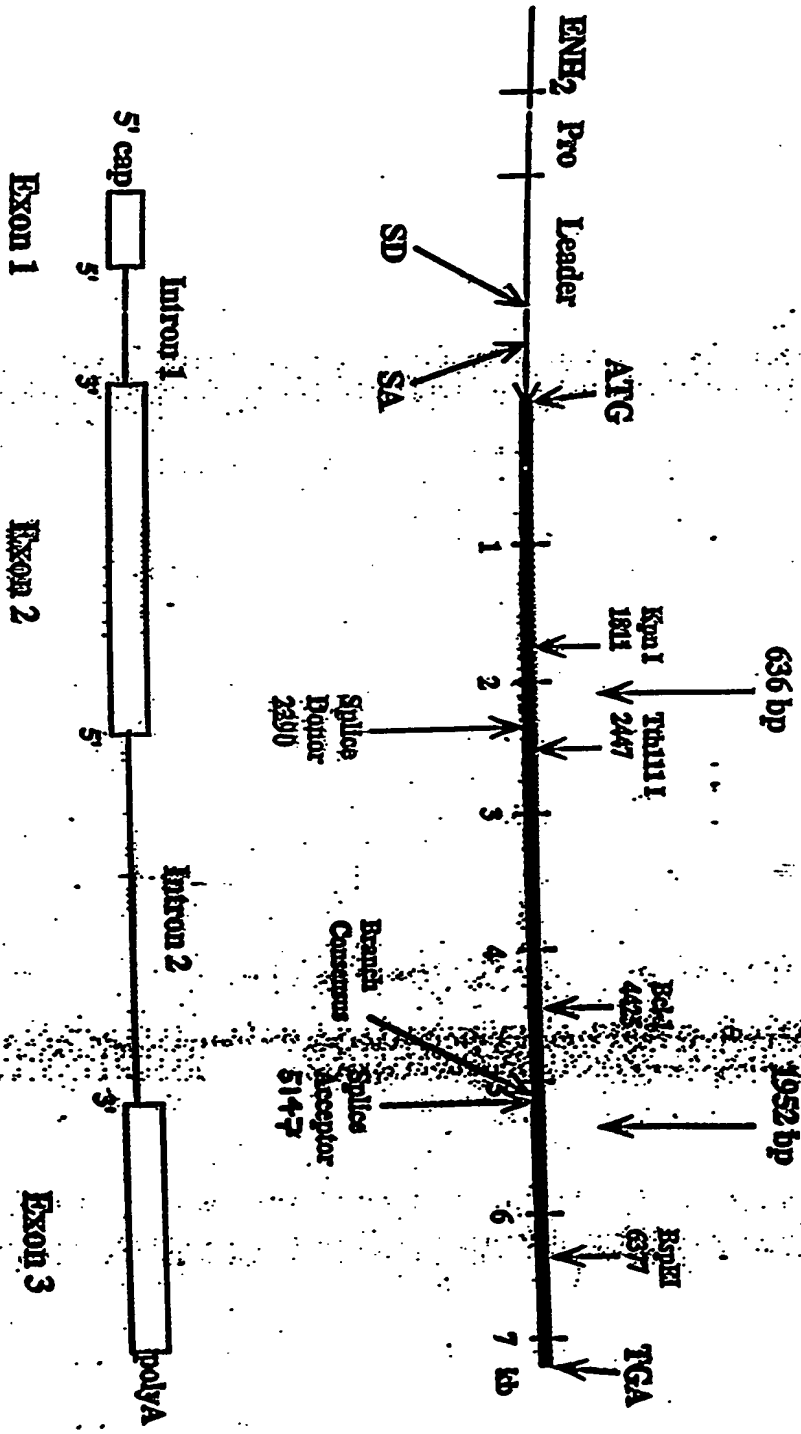


FIG. 13

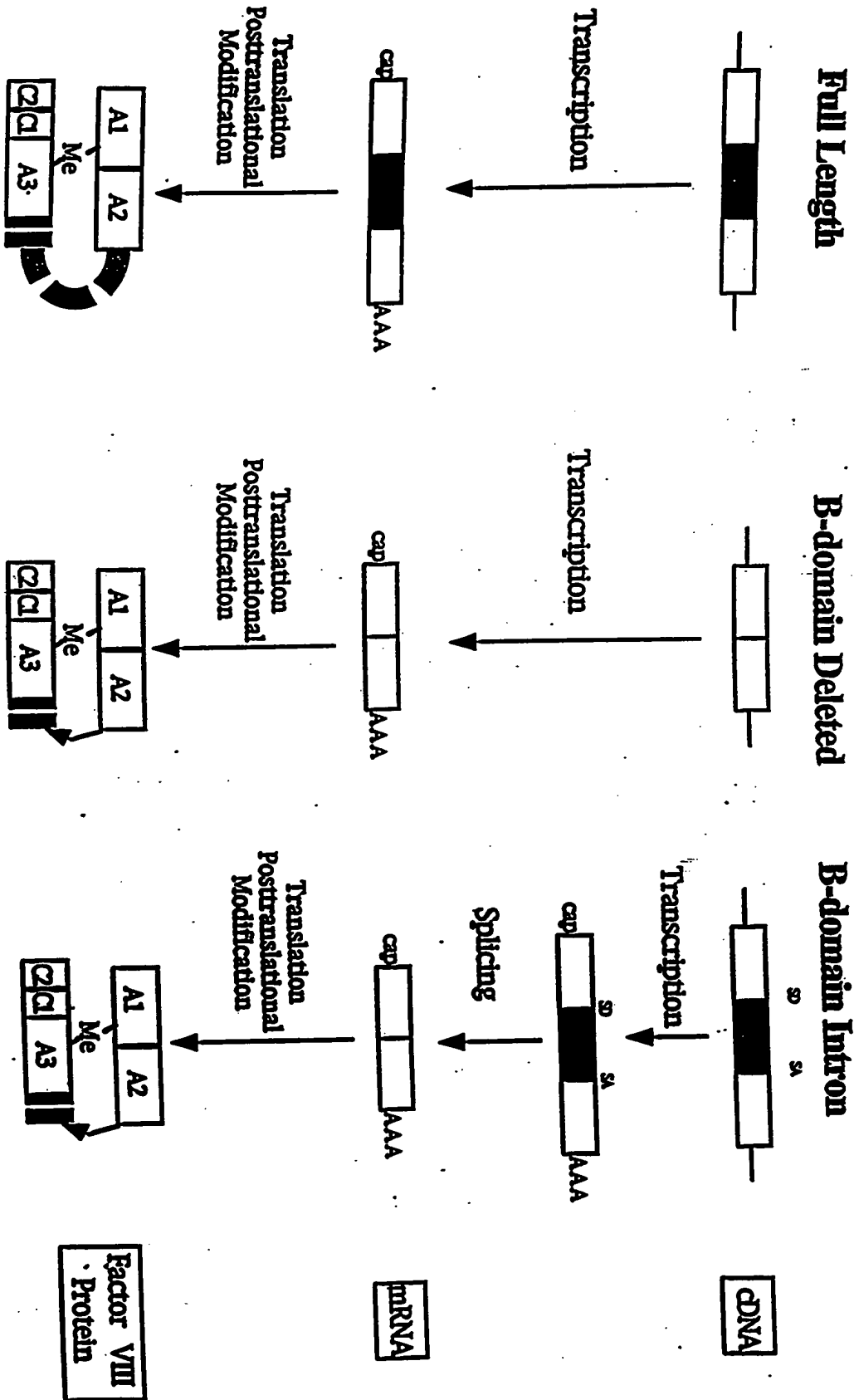


FIG. 14

**Relative Expression Levels of
Factor VIII Plasmids**

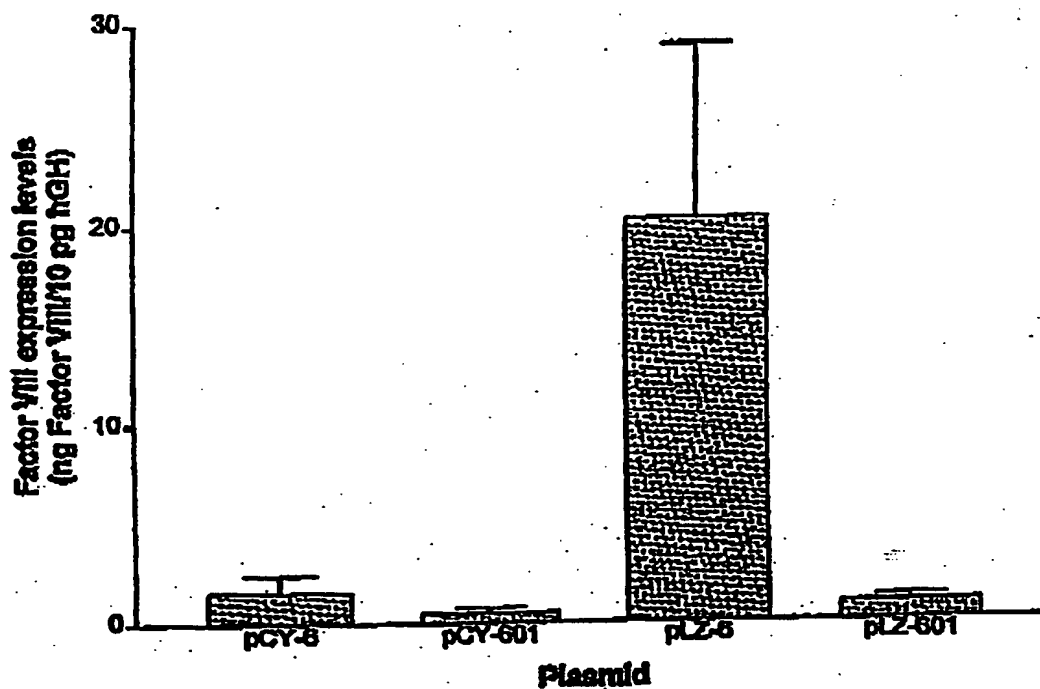


FIG. 15

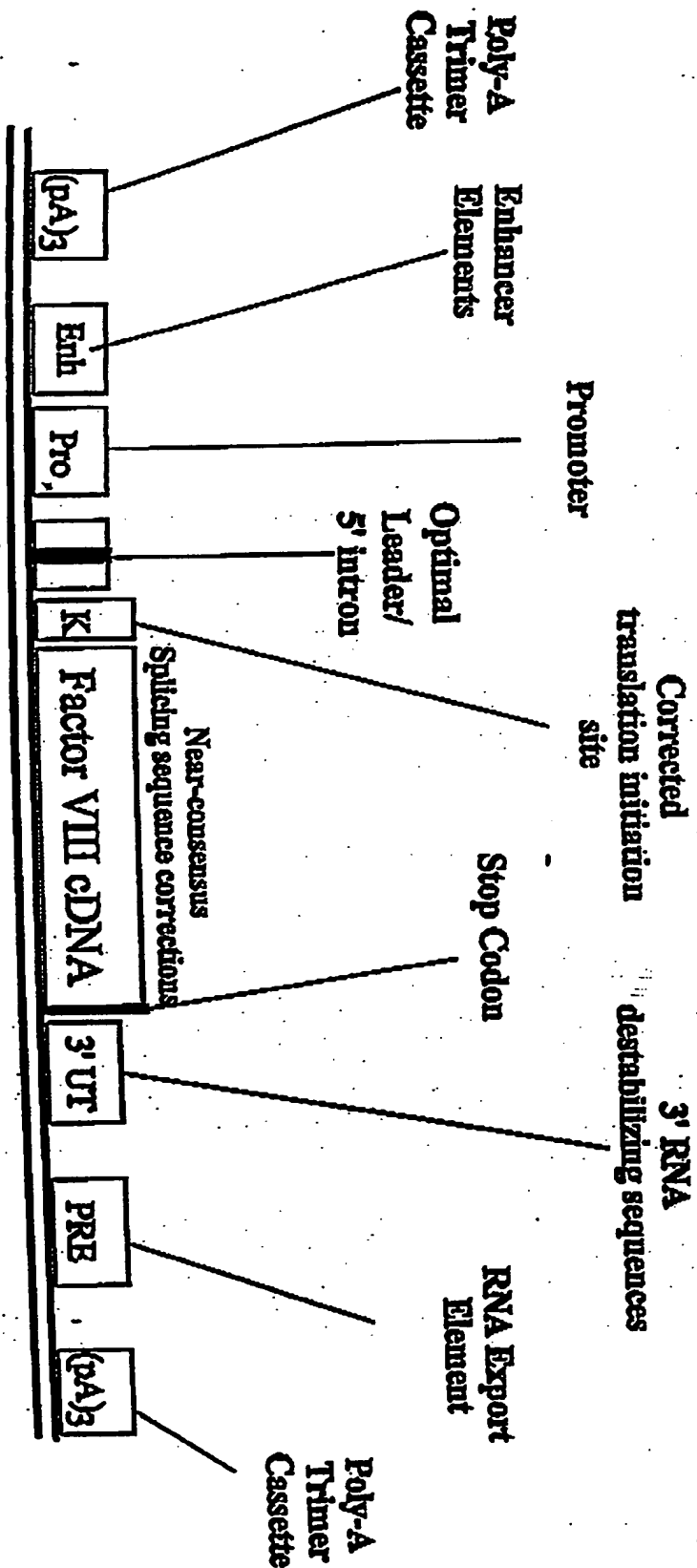


FIG. 16

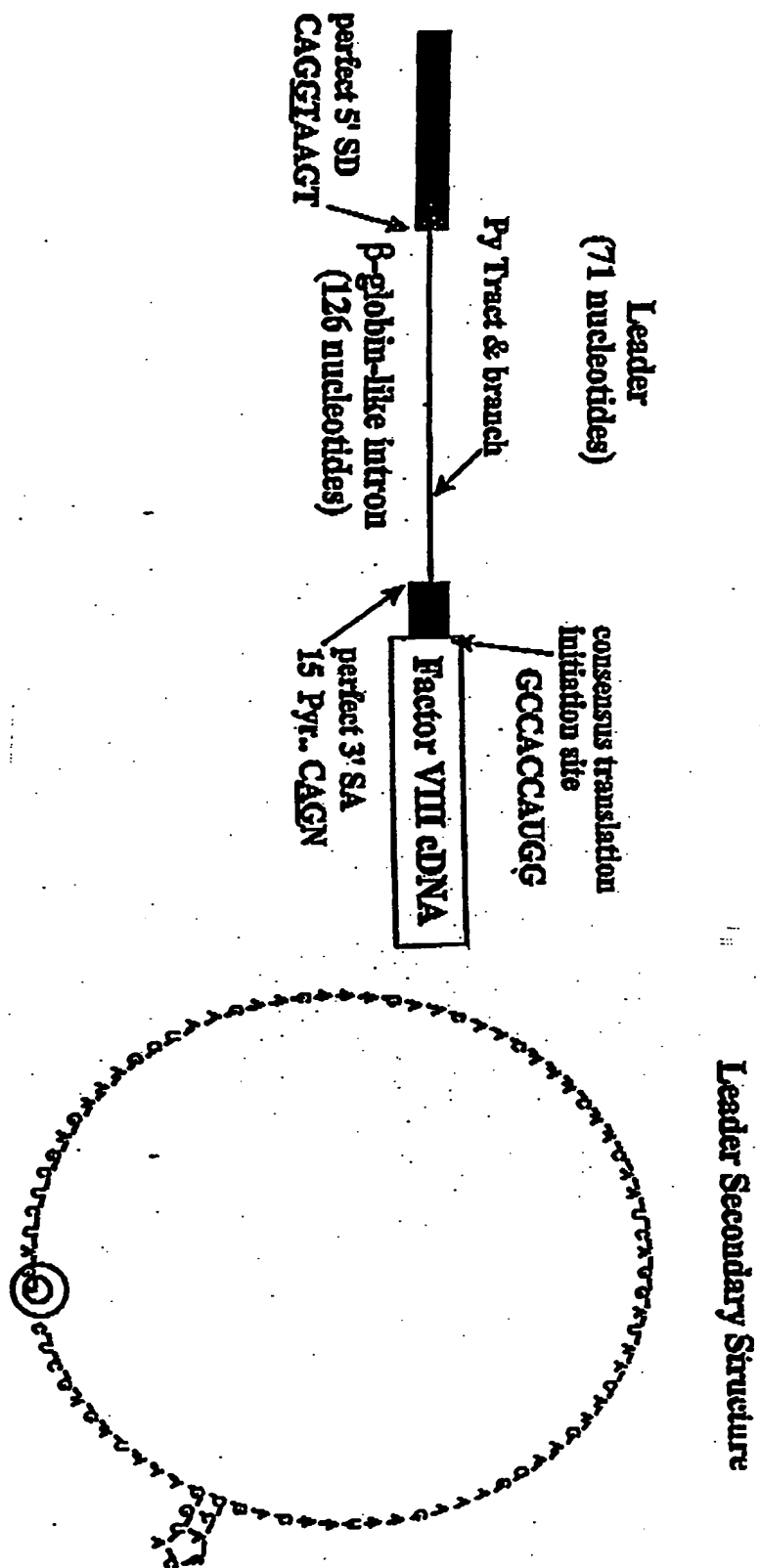


FIG. 17

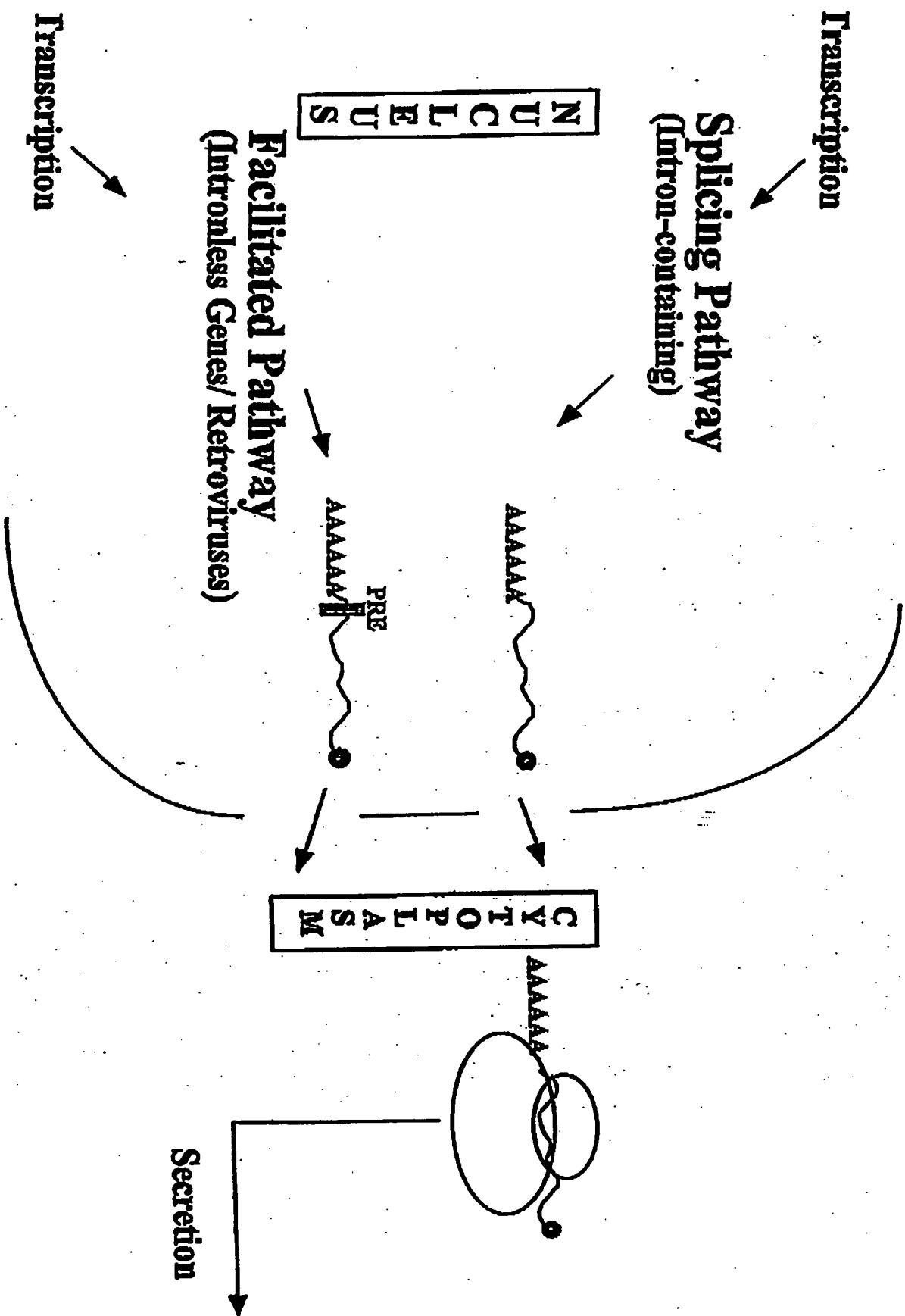
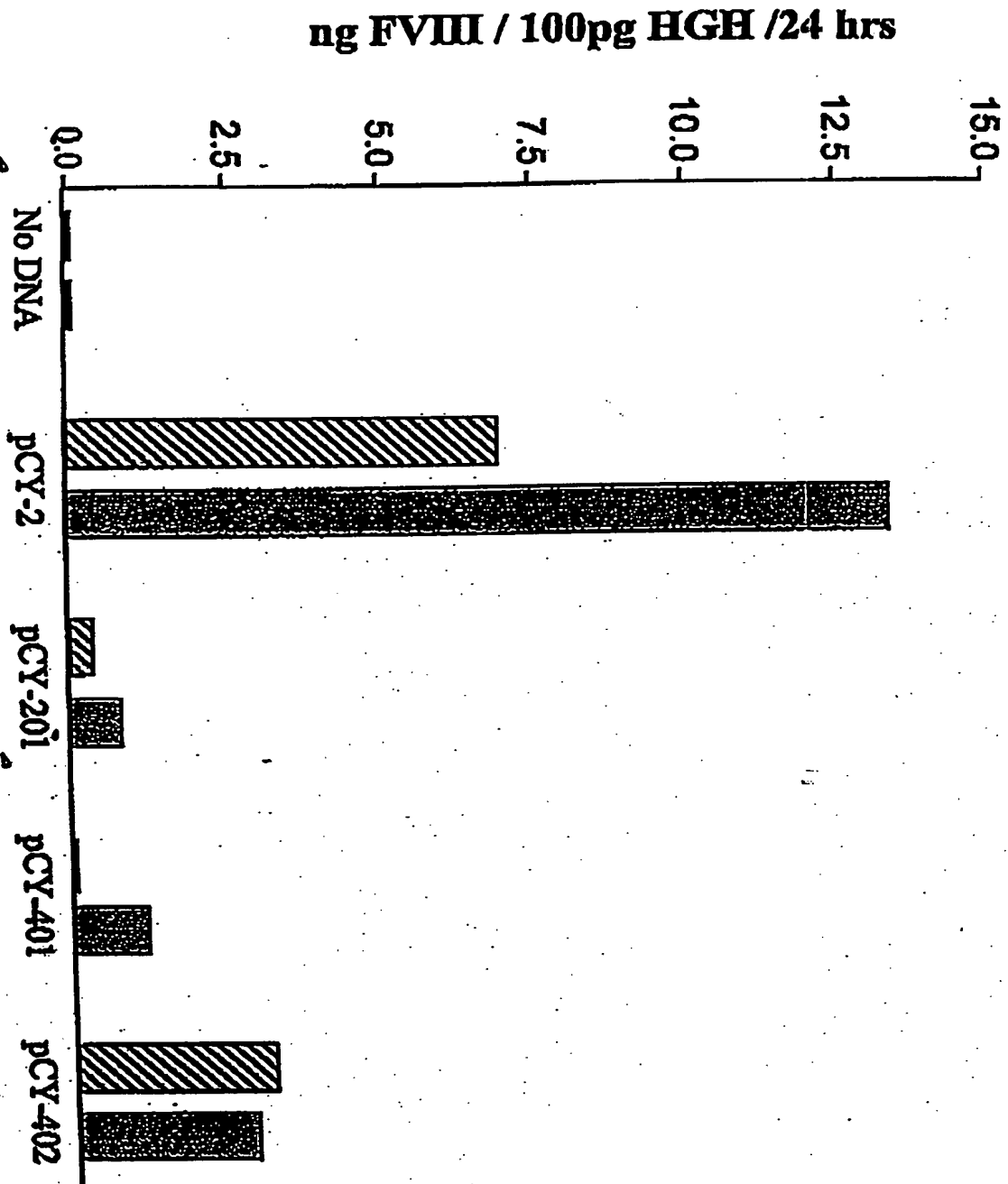


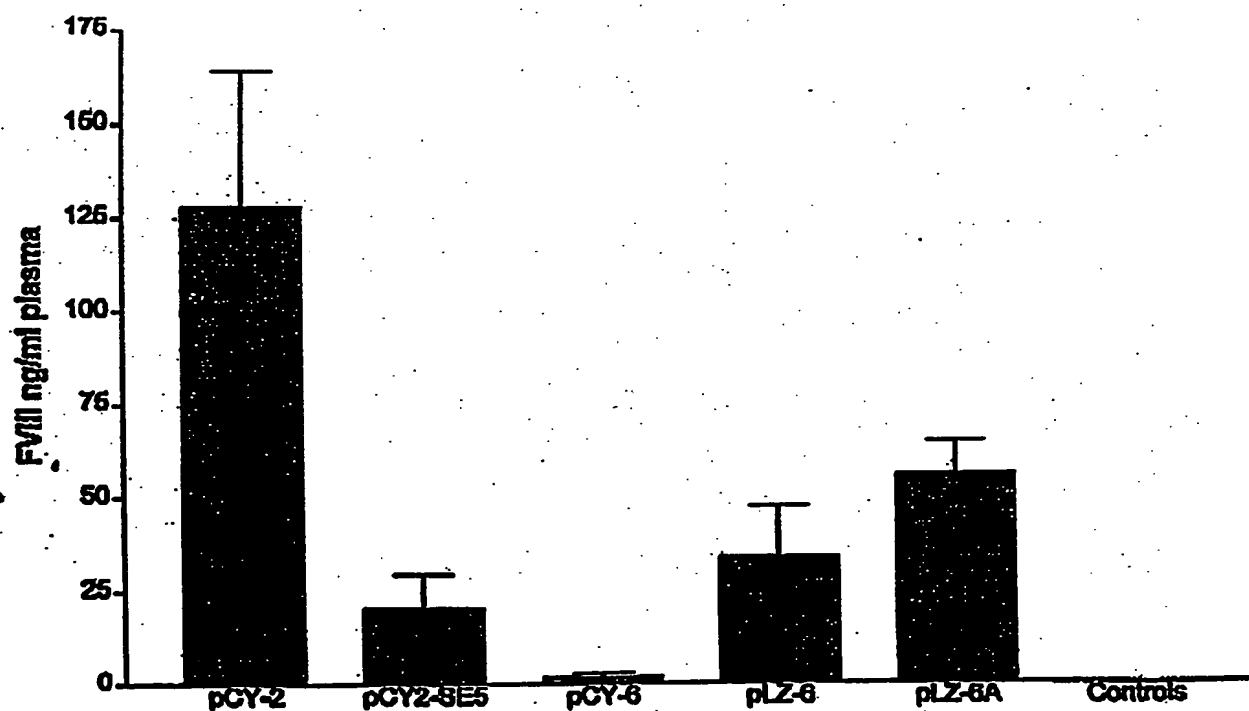
FIG. 18



0053369 042000

FIG. 19

**#889 *in vivo* test
of Factor VIII expression plasmids
Modified Coatest
12-10-97**



A Potent Tissue-specific Enhancer Made of Clustered Liver-specific Elements from the Human Alpha-1 Microglobulin/Bikunin Gene*

FIG. 20

5' AGCTTAATTTTAAAGCACTCAAAAGTCGACGTGGCCCTGGCAGCAT
HNF-1
TTACTCTCTCTGTTTGCTCTGGTTAATAATCTCAGGAGCACAACATTC
HNF-3 HNF-1 HNF-4 HNF-3 3'

From : P. Rouet...J.P. Salier, (1992) J. Biol. Chem 267 No.29, pp. 20765-20773

The Immune Response Corporation

0953368 042000

A 218-bp Fragment of the Human Thyroxin-Binding Globulin (TBG) Gene Contains Full Promoter Activity

FIG. 21

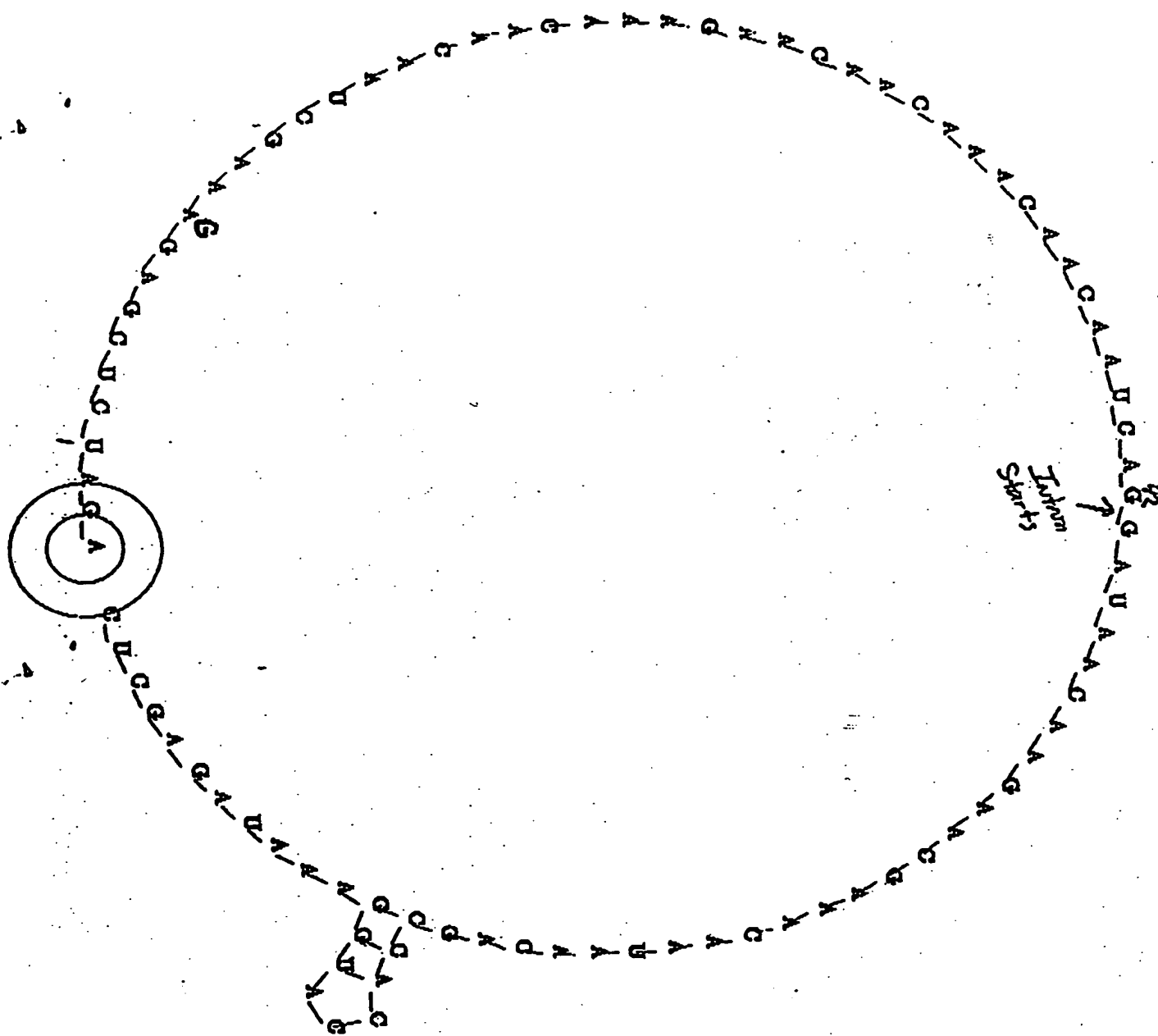
CTTCTCT TTTCTTTAC ATGAA GGGCTGGCAGCCAA GCAAT CACT CAAAGTTCAA
CCTATCAAT TTTGCTTGT TCCTCTGG CCTGGTTTG TACATCAG CTTGAAAT
ACCATCCAG GGTAAATGCT GGG GTTAATTATAAC TAAGAGTGTCTAG TTT GCAAT
ACAGGACATGC TATAA AATGGAAGATGTTGCTTCTGAGAGATA
5 3'

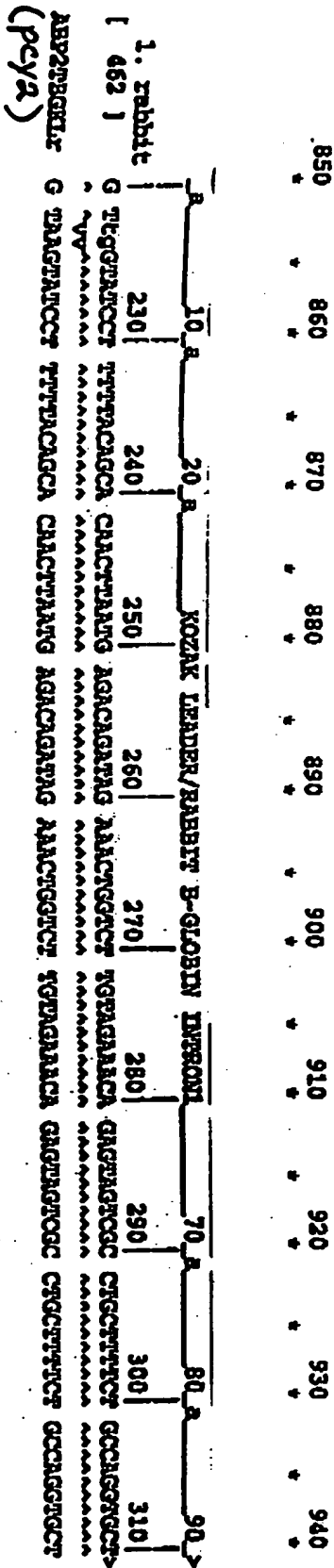
From : Y. Hayashi.....S. Refetoff. (1993). Molec. Endo. 7 No. 8, pp. 1049-1060

The Immune Response Corporation

0053358 042000

FIG. 22

[illegible]



1. rabbit
[462]
ABP2TBGRT G TAGTATCT TTTACAGCA CACTTATG AGACATATG AACTGCTCT TGTAGAACCA GAGTAGTCC CTTCTTCTT CCTAGTCTT

Endothelium-Specific Promoters and Enhancers

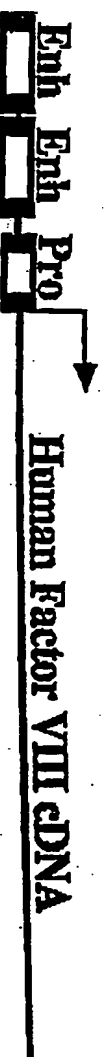


FIG. 24

Promoter Name	Characteristics	Reference
1) Endothelin-1	204 bp; has enhancer seq, TATAA box, TS mapped	Lee et. al. <i>JBC</i> 265 No. 18, 1990. ←
2) Flt-1 (fms-like tyrosine kinase)	~1 kb, no enhancer, TATAA box, TS mapped	Morishita et. al. <i>JBC</i> 270 No. 46, 1995
3) Nitric Oxide Synthase	~1 kb, GATAA box, TS mapped	Zhang et. al. <i>JBC</i> 270 No 25, 1995
Enhancers		
1) c-Fos SRE	60 nt's, non-tissue specific, active in resting or dividing cells	Treisman, <i>Cell</i> 46, 1986 ←
2) hTF/mTie-2	Hybrid design, 72 nt's, all endo's	1998

FIG. 25

Human Factor VIII In Vivo Expression Viral vs Tissue-Specific Promoter

